## REMARKS

Claims 1-30 are pending in the application.

The specification has been amended to add sequence identifiers to the sequences set forth on page 56. The Sequence Listing has been amended to reflect the additional sequences set forth on page 56.

No new matter has been added.

Upon entry of the present amendment, claims 1-30 will be pending.

### Sequence Requirements

The Office alleges that the application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 because "Page 54 of the specification discloses nucleotide sequences that lack associated SEQ ID NO's." Applicants were unable to locate such nucleotide sequences on page 54. However, Applicants were able to locate nucleotide sequences on page 56 which may be subject to the requirements of 37 C.F.R. §§ 1.821-1.825. Applicants note that the sequences on page 56 were shown for the purposes of illustrating oligonucleotide duplexes but are not claimed. Notwithstanding, Applicants have amended the specification to assign SEQ ID NOS: to the sequences on page 56 and attached a replacement sequence listing hereto.

### Restriction Requirement

Claims 1-30 are subject to a restriction requirement. The Examiner required Applicants to elect one of four patentably distinct inventions for examination. Group I, encompassing claims 2-16, 21, 26-30, is said to be drawn to a compound 8-80 nucleobases in length that inhibits the expression of ACE2 mRNA, and is classified in class 536, subclass 24.5.[1] Group II, encompassing claims 17 and 22-23, is said to be drawn to a method of treating an animal by inhibiting the expression of ACE2 in cells or tissues, and is classified in class 514, subclass 44. Group III, encompassing claims 18-19, is said to be drawn to a method of screening for a modulator of ACE2, and is classified in class 435, subclass 6. Group IV, encompassing claim 20,

1 Applicants note that claims 1, 24 and 25 were not assigned to any of Groups I-IV but assume that claims 1, 24 and 25 are properly part of Group I.

is said to be drawn to a method for identifying the presence of ACE2 in a sample, and is classified in class 435, subclass 91.2. The Office, alleging that searching more than one of the sequences recites in claims 20, 24 or 25 "presents an undue burden on the Patent and Trademark Office ...", further requires election of one "oligonucleotide sequence from claims 20, 24 or 25 that corresponds to the target region claimed." (Office Action, page 8). Applicants respectfully traverse and request reconsideration of the Restriction Requirement.

Applicants provisionally elect herein Group I, encompassing claims 1*, 2-16, 21, 24*, 25*, 26-30 and SEQ ID NO:36 for examination. As discussed above, Applicants assume that the SEQ ID NOS marked with a "*" are part of Group I. Applicants note that SEQ ID NO:36 is directed to the coding region of ACE2. Notwithstanding the foregoing, however, as discussed below, Applicants respectfully point out that any restriction requirement of "claims 20, 24 or 25" should be a ***species*** election.

M.P.E.P. §803 mandates two criteria for a proper requirement for restriction: 1) the inventions must be independent or distinct; and 2) there must be a serious burden on the examiner. Applicants respectfully assert that the examination of the four Groups identified by the Office would not present an undue burden on the Office because when the Examiner conducts the search, art including compounds that inhibit expression of ACE2 mRNA (Group 1), methods of inhibiting the expression of ACE2 mRNA (Group 2), methods of screening for a modulator of ACE2 mRNA (Group 3), or methods for identifying the presence of ACE2 in a sample (Group 4) would also be located, ***if*** such art exists.

Accordingly, Applicants respectfully request the examination of Groups I-IV without restriction.

**Restriction of Claims 24 and 25**

The Office alleges that "although the instant antisense sequences claimed in 24 and 25 each target the same gene, the instant antisense sequences are considered to be unrelated, since each antisense sequence claimed... has a unique nucleotide sequence, each antisense sequence targets a different and specific regions of ACE2, and each antisense sequence, upon binding to

ACE2, functionally decreases the expression of the gene to a varying degree." The Office requires that election of one sequence from "claims 20, 24 or 25 that corresponds to the target region claimed." (Office Action page 8).

Preliminarily, Applicants were unable to locate a requirement in the pending Office Action for Applicants to specifically elect a specific target region. Applicants note that Table 2 (starting on page 73 of the application) correlates target region with the SEQ ID NOS set forth in claims 24 and 25.

The Office's reasoning that election of one sequence from claims 20, 24 or 25, however, is clearly not supported by the M.P.E.P., which states:

> Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 *et seq.* Nevertheless, to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has declared *sua sponte* to partially waive the requirements of 37 CFR 1.141 *et seq.* and permit a reasonable number of such nucleotide sequences to be claimed in a single application.

See in §803.04 and *Examination of Patent Applications Containing Nucleotide Sequences*, 1192 O.G. 68 (November 19, 1996).

The procedure for handling applications that include generic claims is set forth in 37 CFR § 1.146. This rule provides that:

> [I]n the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted ***if no claim to the genus is found to be allowable.***

As stated in MPEP § 809.02(a), "upon the allowance of a generic claim, applicant will be

entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR § 1.141." Where generic claims are present, an applicant ***may*** be required to elect a ***species*** for initial examination, but the generic claims are still subject to examination to determine whether such generic claims are allowable.

MPEP § 806.04(b) states that species may be related inventions. Specifically this section of the MPEP directs that:

> [w]here inventions as disclosed and claimed are both (A) species under a claimed genus and (B) related, then the question of restriction ***must*** be determined by both the practice applicable to election of species and the practice applicable to other types of restriction such as those covered in MPEP § 806.05- § 806.05(i). If restriction is improper under either practice, it should not be required.

The species set forth in claims 24 and 25 (particular oligonucleotide sequences) fall within the genus of claim 1 (compounds targeted to a nucleic acid encoding ACE2). The species are also related; each species is a compound which both targets and inhibits the expression of ACE2 by at least 10%. Therefore, as described above, "the question of restriction ***must*** be determined by both the practice applicable to election of species and the practice applicable to other types of restriction such as those covered in MPEP § 806.05- § 806.05(i)." In the present case, restriction must be determined by the practice applicable to election of species.

The practice applicable to the types of restriction such as those covered in MPEP § 806.05- § 806.05(i) is clearly not relevant to the present invention; these sections of the MPEP discuss related inventions, including "Combination and Subcombination or Element", "Old Combination – Novel Subcombination", "Criteria of Distinctness for Combination, Subcombination, or Element of a Combination", "Subcombinations Usable Together", "Process and Apparatus for Its Practice – Distinctness", "Process of Making and Product Made – Distinctness", "Apparatus and Product Made – Distinctness", "Product and Process of Using", and "Product, Process of Making, and Process of Using – Product Claim Not Allowable."

As MPEP § 806.04(b) states that species that are related inventions ***must*** be determined by both the practice applicable to election of species and the practice applicable to other types of restriction such as those covered in MPEP § 806.05- § 806.05(i) ***and*** as the rules detailed by

MPEP § 806.05- § 806.05(i) are not relevant to the present invention, Applicants respectfully assert that the restriction requirement the Office has levied against claims 20, 24 and 25 should instead be an election of species requirement.

The nucleotide sequences in claims 24 and 25 are related to one another and do not encode different proteins. Furthermore, the claimed sequences of claims 24 and 25 are so closely related that a search an examination of the entire claim can be made without serious burden; all species listed in claims 24 and 25 have a common characteristic in that they "demonstrated at least 36% inhibition of human ACE2 expression" (page 74 of the specification of the instant application).

Even assuming *arguendo* that each nucleotide sequence in claims 24 and 25 was not related and did encode different proteins, the Commissioner nonetheless authorized the examination of up to 10 ***un***related nucleotide sequences. Because the sequences are related and encode the same protein, Applicants assert that at least 10 sequences should be examined.

So, even though the Office acknowledges that the Commissioner has specifically waived partially the requirement of 37 C.F.R. 1.141 to permit the examination of "up to 10 independent and distinct nucleotide sequences in a single application", the Office has asserted that examining "more than one of the instant sequences" presents an undue burden, even when the claimed sequences encode the same protein. The Office has failed, however, to provide any explanation why: 1) one is a reasonable number (as opposed to two, three, four, five, etc.); and 2) in which circumstances would the "reasonable number" be a number closer to ten.

Applicants respectfully assert that it appears that the Office's practice in this regard vitiates the Commissioner's explicit waiver. Applicants point out that if it is the Office's position that the Commissioner's waiver is no longer in effect, public notice and an opportunity for public comment should be provided.

Applicants respectfully requests that the Office examine more than a single nucleotide sequence or, alternatively, justify its decision not to follow the Commissioner's explicit waiver.